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Treatment effects of renin-angiotensin system inhibitor and calcium channel blocker in patients with coronary artery narrowing (from the Japanese Coronary Artery Disease Study)

Running Head: Combining RAS Inhibitor and CCB

by
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Abstract

Low dose antihypertensive drugs in combination are prescribed frequently in clinical practice. Combination treatment is superior to monotherapy with higher doses of each drug in terms of blood pressure reduction and side effects. However, it is unclear whether combination treatment provides additional prognostic benefit beyond the blood pressure lowering effects. We assessed the usefulness of the combined treatment of a renin-angiotensin system inhibitor (RASI) and a calcium channel blocker (CCB) for all cardiovascular events in the Japanese Coronary Artery Disease (JCAD) Study population. In the JCAD Study, which is an observational and non-randomized trial, 13,812 patients with angiographically shown narrowing > 50% in ≥ 1 of 3 major coronary arteries were followed up for a mean of 2.7 years. The primary endpoint of the study was all cardiovascular events. In the present study, baseline covariates possibly influencing the event rate were adjusted between the different treatment groups. There was no statistically significant difference in the event rate between the RASI monotherapy and combined treatment groups, although Kaplan-Meier analysis showed a 23% ($p = 0.0003$) relative risk reduction with an RASI monotherapy compared with the control group. In conclusion, there may be no additional benefit beyond blood pressure lowering effects in combination of an RASI and a CCB in patients with angiographically documented CAD.

Key words Calcium channel blocker · Combination therapy · Coronary artery disease · Renin-angiotensin system inhibitor

Introduction

It is well known that the use of antihypertensive agents in combination provides a synergistic or at least an additive blood pressure reduction, which is greater than higher doses of each drug used as monotherapy.[1-4] Combination low dose drug treatment also reduces side effects.[1, 2] The combination of a renin-angiotensin system inhibitor (RASI) and a calcium channel blocker (CCB) is frequently used in clinical practice.[5] Since both an RASI and a CCB possibly provide cardiovascular protection by improving vascular function,[6-8] it is postulated that combination therapy might provide prognostic benefit beyond the blood pressure lowering effects. Thus, we compared prognostic effects of an RASI and a CCB alone or in combination beyond the blood pressure lowering effects after adjustment for baseline covariates including the blood pressure in the Japanese Coronary Artery Disease (JCAD) Study population.[9]

Materials and methods

The protocol and major outcomes of the JCAD study were previously published.[9] Briefly, we consecutively enrolled patients with angiographically demonstrable narrowing > 50% in ≥ 1 of 3 major coronary arteries. Initially, 15,628 patients were registered and 13,812 patients were followed up for a mean of 2.7 years (follow-up rate 88.4%). Clinical events to be registered in the database were defined as all-cause deaths, including cardiac, cerebral,

vascular and other deaths, and cerebral, cardiac and vascular events. Cerebral events included cerebral hemorrhage, cerebral infarction and transient ischemic attack. Cardiac events consisted of fatal and nonfatal myocardial infarction, unstable angina, congestive heart failure, coronary bypass graft surgery, resuscitated cardiac arrest, and cardiopulmonary arrest on arrival. Angiographic restenosis incidentally found during routine follow-up coronary angiography without clinical symptoms was excluded from events registration. Aortic dissection and rupture of an aortic aneurysm were classified as vascular events. The primary endpoint of the present study was all cardiovascular events. The data of this study was derived from a post-hoc analysis of an observational, non-randomized trial.

Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Statistical analysis

Numerical data are presented as the mean value ± SD. Unpaired Student's t-test was applied for the comparison of parametric values, while comparisons of variables between the 2 groups were made by the Wilcoxon test for non-parametric unpaired values. Proportional data were analyzed by the chi-square test. Propensity score matching analysis was used to match baseline characteristics between the 2 groups.[10] Kaplan-Meier hazard ratios were used to

examine the incidence over time, and the log-rank test was used to assess group differences. Two-sided $p < .05$ was regarded as statistically significant.

Results

As shown in Table 1, baseline covariates potentially influencing the cardiovascular event were adjusted between the 2 groups by the propensity score matching method. However, systolic blood pressure was slightly but significantly higher (1.3 mmHg in mean) in the control group than the RASI monotherapy group (Table 1-A), and was slightly but significantly lower (1.9 mmHg in mean) in the control group than the combination treatment group (Table 1-C). It was also significantly lower (3.1 mmHg in mean) in the RASI monotherapy group than the combination treatment group (Table 1-D). Kaplan-Meier analysis showed a 23% relative risk reduction of all cardiovascular events with the RASI monotherapy compared with the control group. Log-rank test showed a statistically significant difference ($p = 0.0003$) in the event rate between the 2 groups (Fig. 1A). Meanwhile, there was no statistically significant difference in the incidence of all cardiovascular events between the control and the CCB monotherapy groups (Fig. 1B). Furthermore, no statistically significant difference in the incidence of all cardiovascular events was observed between the control and combination treatment groups (Fig. 1C). There was also no statistically significant difference in the incidence of all cardiovascular events between the RASI monotherapy and combination

treatment groups (Fig. 1D).

Cumulative hazard analysis of endpoints of subcategories revealed similar results of the composite endpoint. Cerebral events in the RASI monotherapy group was significantly lower than the combination treatment group (Table 2).

Table 3 shows follow-up blood pressure levels in each group. There were slight but significant differences in the systolic blood pressure levels between the combination treatment group and the untreated control or RASI monotherapy group over the 3 years follow-up periods.

Discussion

In the current study, baseline covariates, including coronary risk factors such as hypertension, hyperlipidemia, impaired glucose tolerance and tobacco use were adjusted between the control and treatment groups by the propensity score matching method.[10] As a result, additional effects beyond blood pressure lowering of an RASI and a CCB alone, or in combination were successfully evaluated. The findings of this study suggest that the usefulness of combination of an RASI and a CCB beyond blood pressure lowing may not exist. This implies that the beneficial effects of the combination treatment with an RASI and a CCB compared with each monotherapy are largely due to the blood pressure lowering effects. In previous studies indicating the usefulness of combination therapy, blood pressure

levels were significantly lower in the combination treatment.[1-4] Thus, there may be no additional beneficial effects of combination of an RASI and a CCB. This may be explained, at least in part, by the difference between the clinical situation and experimental study where more than ten-fold dose of a CCB was used to unravel the vascular protective effect of the drug.[7] Although the RASI monotherapy was effective in terms of the prevention of cardiovascular events, the reason why the significantly favorable effect of an RASI disappeared by addition of a CCB is unclear. The slight but significantly higher blood pressure in the combination treatment group as compared with the untreated control and RASI monotherapy groups may have counterbalanced the effectiveness of the combination treatment. Thus, there is a possibility that “reversal of cause and effect” may have brought about in the present study.

In the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[11], 5137 hypertensive patients with diabetes mellitus were randomized to amlodipine with addition of perindopril or atenolol with addition of thiazide, and were followed-up for 5 years. The amlodipine-based treatment reduced the incidence of total cardiovascular events and procedures by 14% compared with the atenolol-based treatment. The mean systolic and diastolic pressures were 3.0 mmHg and 1.9 mmHg lower among those on the amlodipine-based treatment. Blood levels of glucose, creatinine and triglyceride throughout the study were significantly higher among patients on the atenolol-based treatment.

Above-mentioned differences between the 2 treatment arms may explain the superiority of the combination of a CCB with an RASI to that of a beta-blocker with a diuretic.

In the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial,[12] it has been demonstrated that the benazepril-amlodipine combination treatment is superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in high risk patients with hypertension (relative risk reduction; 19.6%, $p < 0.001$). Mean blood pressure after dose adjustment was significantly lower in the benezepril-amlodipine group compared with the benazepril-hydrochlorothiazide group. The mean difference in blood pressure between the two groups was 0.9 mmHg systolic and 1.1 mmHg diastolic. A small but significant difference in blood pressure may explain the superiority of the benezepril-amlodipine group. Alternatively, the combination of a CCB with an RASI may provide unique beneficial effects beyond the blood pressure lowering effects as compared to the combination of an RASI with a diuretic.

There are several limitations to the present study. First, it is likely that there is a bias that relates to individuals in this cohort treated with an RASI and/or a CCB, being more severely ill than others. However, despite this residual bias, the hazard ratios tended to be lower in each of the drug treated group compared to the untreated control group (Fig 1-A, B, C). Above-mentioned bias inherent to the observational study may have obviated the

difference between the RASI monotherapy and combination treatment groups, because complete matching regarding risk factors, exercise,[13] drug usage[14] and severity of diseases between the 2 groups is difficult due to the limitation of the propensity score matching (Fig 1-D). Second, in this study cohort, the prevalence of patients with hypertension was approximately 50% to 70%, therefore it may be limited to extrapolate these results to patients with hypertension. Finally, the randomization of patients to each treatment arm was not conducted, because the JCAD study was an observational, non-randomized trial. In this meaning, to clarify the usefulness of combination treatment beyond the blood pressure lowering effects, a prospective, randomized trial consisting of an RASI or a CCB monotherapy and the combination treatment groups are needed, although the exact matching of blood pressure levels between the monotherapy and the combination treatment may be difficult. In conclusion, our findings suggest that there may be no additional prognostic benefit beyond blood pressure lowering effects in combination of an RASI and a CCB in patients with CAD.

References

1. Law MR, Wald NJ, Morris JK, Jordan RE (2003) Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. Brit Med J 326:1427-1431

2. Neutel JM, Smith DHG, Weber MA (2001) Low-dose combination therapy: an important first-line treatment in the management of hypertension. Am J Hypertens 14:286-292

3. Flack JM, Calhoun DA, Satlin L, Barbier M, Hilkert R, Brunel P (2009) Efficacy and safety of initial combination therapy with amlodipine/valsartan compared with amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study. J Hum Hypertens Jan 29 [Epub ahead of print]

4. Ge CJ, Lu SZ, Chen YD, Wu XF, Hu SJ, Ji Y (2008) Synergistic effect of amlodipine and atorvastatin on blood pressure, left ventricular remodeling, and C-reactive protein in hypertensive patients with primary hypercholesterolemia. Heart Vessels 23:91-95

5. Kuschair E, Acura E, Sevilla D (1996) Treatment of patients with essential hypertension: Amlodipine 5 mg/benazepril 20 mg compared with amlodipine 20 mg and placebo. Clin Ther 18:6-12

6. Wassmann S, Stumpf M, Strehlow K, Schmid A, Schieffer B, Böhm M, Nickenig G (2004) Interleukin-6 induces oxidative stress and endothelial dysfunction by overexpression of the angiotensin II type 1 receptor. Circ Res 94:534-541

7. Zhang X, Hintze TH (1998) Amlodipine releases nitric oxide from canine coronary microvessels: an unexpected mechanism of action of a calcium channel-blocking agent. Circulation 97:576-580

8. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Koh Y, Shin EK (2008) Distinct vascular and metabolic effects of different classes of anti-hypertensive drugs. Int J Cardiol Dec 5 [Epub ahead of print]

9. The Japanese Coronary Artery Disease (JCAD) Study Investigators (2006) Current status of the background of patients with coronary artery disease in Japan: the Japanese Coronary Artery Disease Study (The JCAD Study). Circ J 70:1256-1262

10. D'Agostino RB Jr (1998) Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 17:2265-2281

11. Östergren J, Poulter NR, Sever PS, Dahlöf B, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, for the ASCOT investigators (2008) The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. J Hypertens 26:2103-2111

12. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ, ACCOMPLISH Trial Investigators (2008) Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med

359:2417-2428

13. Mourad JJ, Danchin N, Puel J, Gallois H, Msihid J, Safar ME, Tanaka H (2008) Cardiovascular impact of exercise and drug therapy in older hypertensives with coronary heart disease: PREHACOR study. Heart Vessels 23:20-25

14. Fujita M, Yamazaki T, Hayashi D, Kohro T, Okada Y, Nagai R, for The JCAD Study Investigators (2007) Comparison of cardiovascular events in patients with angiographically documented coronary narrowing with combined renin-angiotensin system inhibitor plus statin versus renin-angiotensin system inhibitor alone versus statin alone (from the Japanese Coronary Artery Disease Study). Am J Cardiol 100:1750-1753

Figure Legend

Figure 1.

Cumulative hazard of all cardiovascular events in patients not receiving an RASI and a CCB and those receiving an RASI but no CCB (A), a CCB but no RASI (B), and both an RASI and a CCB (C). Cumulative hazard of all cardiovascular events in patients receiving an RASI but no CCB and those receiving both an RASI and a CCB (D).

CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio; RASI = rennin-angiotensin system inhibitor.

Table 1-A

Baseline characteristics of patients after propensity score matching

Variables	No RASI, no CCB	RASI, but no CCB	p value
Patients receiving an RASI, but no CCB			
No. of patients	2,447	2,447	
Age (yrs)	65.5 ± 10.3	64.5 ± 10.0	0.9205
Men	79.1%	78.5%	0.5998
Hypertension	48.6%	49.2%	0.6473
Hyperlipidemia	56.6%	55.9%	0.6040
Impaired glucose tolerance	38.9%	39.6%	0.5983
Body mass index ≥ 25 (kg/m^2)	30.9%	31.2%	0.8288
Tobacco use	43.1%	43.0%	0.9310
Alcohol intake	39.6%	39.7%	0.9534
Family history of coronary artery disease	15.6%	16.0%	0.6952
Heart failure	12.4%	12.0%	0.6620
Left main coronary narrowing	4.4%	4.0%	0.4765
Number of coronary arteries narrowed	1.8 ± 0.8	1.8 ± 0.8	0.9581
Systolic blood pressure (mmHg)	130.5 ± 20.1	129.2 ± 20.2	0.0039
Diastolic blood pressure (mmHg)	74.2 ± 12.1	74.2 ± 12.2	0.5275
Total cholesterol (mg/dl)	195.9 ± 39.0	196.8 ± 38.1	0.3549
Fasting blood sugar (mg/dl)	121.5 ± 48.9	122.4 ± 48.4	0.1442
Angiotensin-converting enzyme inhibitors	0%	71.6%	0.0000
Angiotensin receptor blockers	0%	30.3%	0.0000

Values are the mean ± SD or percentage of each characteristic.

CCB = calcium channel blocker; RASI = renin-angiotensin system inhibitor; Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; Hyperlipidemia was defined as total cholesterol ≥ 220 mg/dl or low density lipoprotein cholesterol ≥ 140 mg/dl or triglyceride ≥ 150 mg/dl.

Table 1-B

Baseline characteristics of patients after propensity score matching

Variables	No RASI, no CCB	CCB, but no RASI	p value
Patients receiving a CCB, but no RASI			
No. of patients	2,659	2,659	
Age (yrs)	65.3 ± 9.9	65.3 ± 9.7	0.8263
Men	77.5%	77.5%	0.9476
Hypertension	50.2%	50.0%	0.8909
Hyperlipidemia	57.4%	57.6%	0.9116
Impaired glucose tolerance	38.2%	39.5%	0.3680
Body mass index ≥ 25 (kg/m^2)	31.1%	32.1%	0.4259
Tobacco use	37.8%	37.3%	0.6918
Alcohol intake	38.0%	38.6%	0.6517
Family history of coronary artery disease	15.9%	15.4%	0.6238
Heart failure	7.0%	7.0%	0.9572
Left main coronary narrowing	5.3%	5.2%	0.9510
Number of coronary arteries narrowed	1.8 ± 0.8	1.8 ± 0.8	0.7075
Systolic blood pressure (mmHg)	131.5 ± 20.1	131.9 ± 18.2	0.3305
Diastolic blood pressure (mmHg)	74.2 ± 12.0	74.3 ± 11.8	0.9703
Total cholesterol (mg/dl)	197.7 ± 39.1	197.9 ± 38.4	0.7003
Fasting blood sugar (mg/dl)	120.9 ± 47.4	120.0 ± 44.9	0.6105

Values are the mean ± SD or percentage of each characteristic.

CCB = calcium channel blocker; RASI = renin-angiotensin system inhibitor; Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; Hyperlipidemia was defined as total cholesterol ≥ 220 mg/dl or low density lipoprotein cholesterol ≥ 140 mg/dl or triglyceride ≥ 150 mg/dl.

Table 1-C

Baseline characteristics of patients after propensity score matching

Variables	No RASI, no CCB	RASI and CCB	p value
Patients receiving an RASI and a CCB			
No. of patients	1,903	1,903	
Age (yrs)	65.5 ± 9.7	65.6 ± 9.5	0.6973
Men	75.8%	76.0%	0.8795
Hypertension	69.8%	69.8%	1.0000
Hyperlipidemia	58.5%	58.8%	0.8434
Impaired glucose tolerance	41.6%	42.3%	0.6694
Body mass index ≥ 25 (kg/m^2)	34.7%	34.4%	0.8647
Tobacco use	38.3%	38.5%	0.8940
Alcohol intake	39.0%	38.5%	0.7393
Family history of coronary artery disease	15.7%	16.2%	0.6582
Heart failure	9.9%	9.7%	0.8701
Left main coronary narrowing	4.2%	4.6%	0.4763
Number of coronary arteries narrowed	1.8 ± 0.8	1.8 ± 0.8	0.2933
Systolic blood pressure (mmHg)	134.9 ± 20.9	136.8 ± 21.0	0.0375
Diastolic blood pressure (mmHg)	75.6 ± 12.3	75.7 ± 12.6	0.5903
Total cholesterol (mg/dl)	197.3 ± 38.6	197.2 ± 36.8	0.8362
Fasting blood sugar (mg/dl)	123.9 ± 49.8	121.2 ± 46.2	0.4278
Angiotensin-converting enzyme inhibitors	0%	71.4%	0.0000
Angiotensin receptor blockers	0%	31.1%	0.0000

Values are the mean ± SD or percentage of each characteristic.

CCB = calcium channel blocker; RASI = renin-angiotensin system inhibitor; Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; Hyperlipidemia was defined as total cholesterol ≥ 220 mg/dl or low density lipoprotein cholesterol ≥ 140 mg/dl or triglyceride ≥ 150 mg/dl.

Table 1-D

Baseline characteristics of patients after propensity score matching

Variables	RASI, but no CCB	RASI and CCB	p value
Patients receiving an RASI and a CCB			
No. of patients	1,901	1,901	
Age (yrs)	65.2 ± 9.6	65.3 ± 9.5	0.9449
Men	76.9%	77.1%	0.8472
Hypertension	69.4%	69.9%	0.7778
Hyperlipidemia	56.8%	57.9%	0.4911
Impaired glucose tolerance	43.0%	42.6%	0.7932
Body mass index ≥ 25 (kg/m^2)	34.1%	34.0%	0.9454
Tobacco use	42.1%	41.8%	0.8695
Alcohol intake	40.9%	41.5%	0.7170
Family history of coronary artery disease	16.8%	17.1%	0.7623
Heart failure	12.5%	13.2%	0.5281
Left main coronary narrowing	3.5%	3.7%	0.7287
Number of coronary arteries narrowed	1.8 ± 0.8	1.8 ± 0.8	0.9997
Systolic blood pressure (mmHg)	133.6 ± 21.1	136.7 ± 21.4	0.0000
Diastolic blood pressure (mmHg)	75.8 ± 12.9	75.7 ± 12.7	0.7263
Total cholesterol (mg/dl)	195.2 ± 37.6	195.6 ± 36.5	0.9230
Fasting blood sugar (mg/dl)	124.0 ± 50.0	121.5 ± 46.8	0.2644
Angiotensin-converting enzyme inhibitors	70.2%	72.1%	0.1977
Angiotensin receptor blockers	31.8%	30.5%	0.3812

Values are the mean ± SD or percentage of each characteristic.

CCB = calcium channel blocker; RASI = renin-angiotensin system inhibitor; Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; Hyperlipidemia was defined as total cholesterol ≥ 220 mg/dl or low density lipoprotein cholesterol ≥ 140 mg/dl or triglyceride ≥ 150 mg/dl.

Table 2

Cumulative hazard of cardiac and cerebral events

Groups	No. of events	No. of patients	HR	95% CI	p value
Cardiac events					
RASI (–) CCB (–)	336	2,447	0.7487	0.6367-0.8804	0.0005
RASI (+) CCB (–)	260	2,447			
RASI (–) CCB (–)	337	2,659	0.8927	0.7651-1.0415	0.1485
RASI (–) CCB (+)	312	2,659			
RASI (–) CCB (–)	265	1,903	0.9054	0.7615-1.0766	0.2607
RASI (+) CCB (+)	250	1,903			
RASI (+) CCB (–)	216	1,901	1.0790	0.8975-1.2973	0.4185
RASI (+) CCB (+)	240	1,901			
Cerebral events					
RASI (–) CCB (–)	47	2,447	0.6779	0.4321-1.0634	0.0886
RASI (+) CCB (–)	33	2,447			
RASI (–) CCB (–)	49	2,659	0.9433	0.6344-1.4025	0.7731
RASI (–) CCB (+)	49	2,659			
RASI (–) CCB (–)	41	1,903	1.0364	0.6783-1.5834	0.8687
RASI (+) CCB (+)	45	1,903			
RASI (+) CCB (–)	23	1,901	1.9742	1.1864-3.3020	0.0077
RASI (+) CCB (+)	44	1,901			

CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio; RASI = renin-angiotensin system inhibitor.

Table 3

Follow-up blood pressure levels

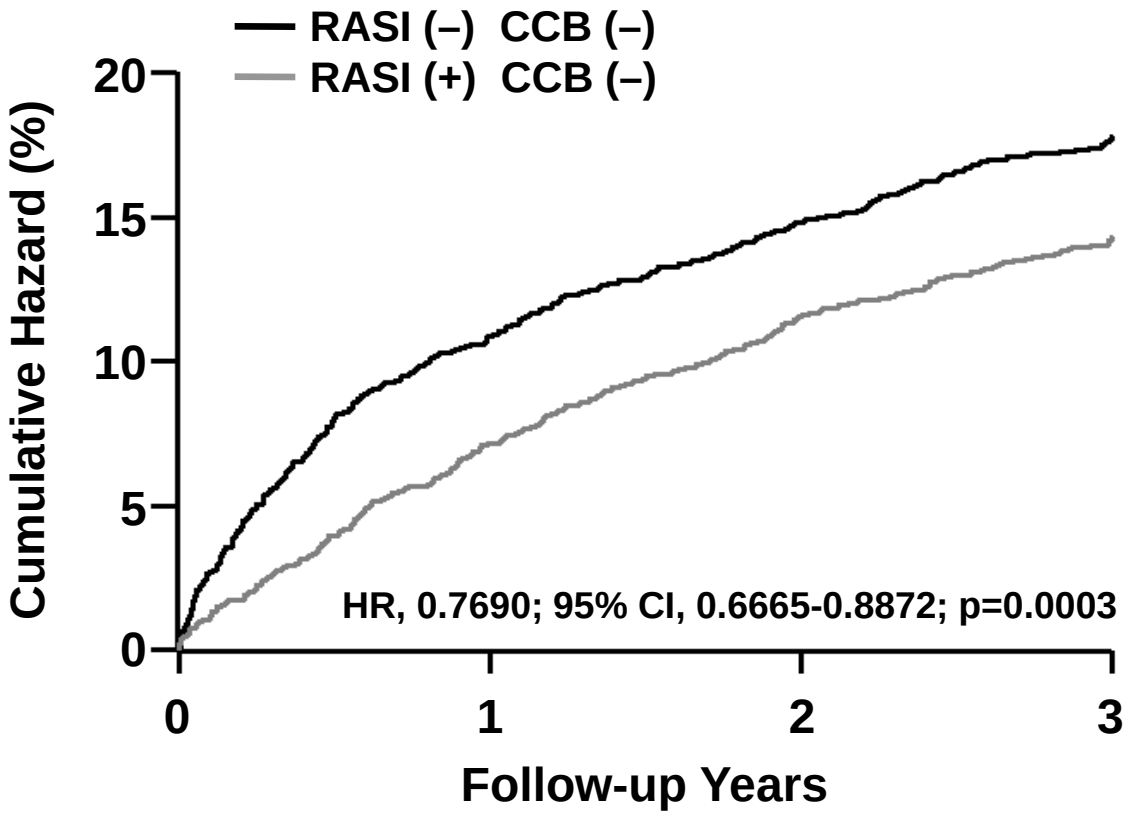
	Baseline	1 Year	2 Years	3 Years
Systolic blood pressure				
RASI (–) CCB (–)	131±20 (n=2,447)	131±18 (n=1,609)	131±17 (n=1,355)	131±17 (n=1,269)
RASI (+) CCB (–)	129±20* (n=2,447)	131±18 (n=2,051)	131±17 (n=1,747)	131±17 (n=1,650)
RASI (–) CCB (–)	132±20 (n=2,659)	131±18 (n=1,754)	131±17 (n=1,462)	131±17 (n=1,383)
RASI (–) CCB (+)	132±18 (n=2,659)	131±17 (n=2,249)	131±17 (n=1,900)	131±16 (n=1,829)
RASI (–) CCB (–)	135±21 (n=1,903)	133±18 (n=1,224)	131±18 (n=1,015)	131±17 (n=961)
RASI (+) CCB (+)	137±21* (n=1,903)	135±18* (n=1,621)	133±18* (n=1,395)	133±17* (n=1,341)
RASI (+) CCB (–)	134±21 (n=1,901)	132±18 (n=1,572)	132±17 (n=1,332)	132±17 (n=1,244)
RASI (+) CCB (+)	137±21† (n=1,901)	136±18† (n=1,611)	134±18† (n=1,388)	134±17† (n=1,335)
Diastolic blood pressure				
RASI (–) CCB (–)	74±12 (n=2,447)	75±11 (n=1,609)	74±10 (n=1,355)	74±11 (n=1,269)
RASI (+) CCB (–)	74±12 (n=2,447)	74±11 (n=2,051)	74±11 (n=1,747)	74±10 (n=1,650)
RASI (–) CCB (–)	74±12 (n=2,659)	74±11 (n=1,754)	74±10 (n=1,462)	74±11 (n=1,383)
RASI (–) CCB (+)	74±12 (n=2,659)	74±10 (n=2,249)	74±10 (n=1,900)	74±10 (n=1,829)
RASI (–) CCB (–)	76±12 (n=1,903)	75±11 (n=1,224)	74±10 (n=1,015)	75±11 (n=961)
RASI (+) CCB (+)	76±13 (n=1,903)	75±11 (n=1,621)	75±11 (n=1,395)	74±11 (n=1,341)
RASI (+) CCB (–)	76±13 (n=1,901)	75±11 (n=1,572)	75±11 (n=1,332)	75±10 (n=1,244)
RASI (+) CCB (+)	76±13 (n=1,901	75±11 (n=1,611)	74±11 (n=1,388)	74±11 (n=1,335)

Values are the mean ± SD.

CCB = calcium channel blocker; RASI = renin-angiotensin system inhibitor.

* $p < 0.05$ vs. RASI (–) CCB (–); †$p<0.05$ vs. RASI (+) CCB (–).

Figure 1-A



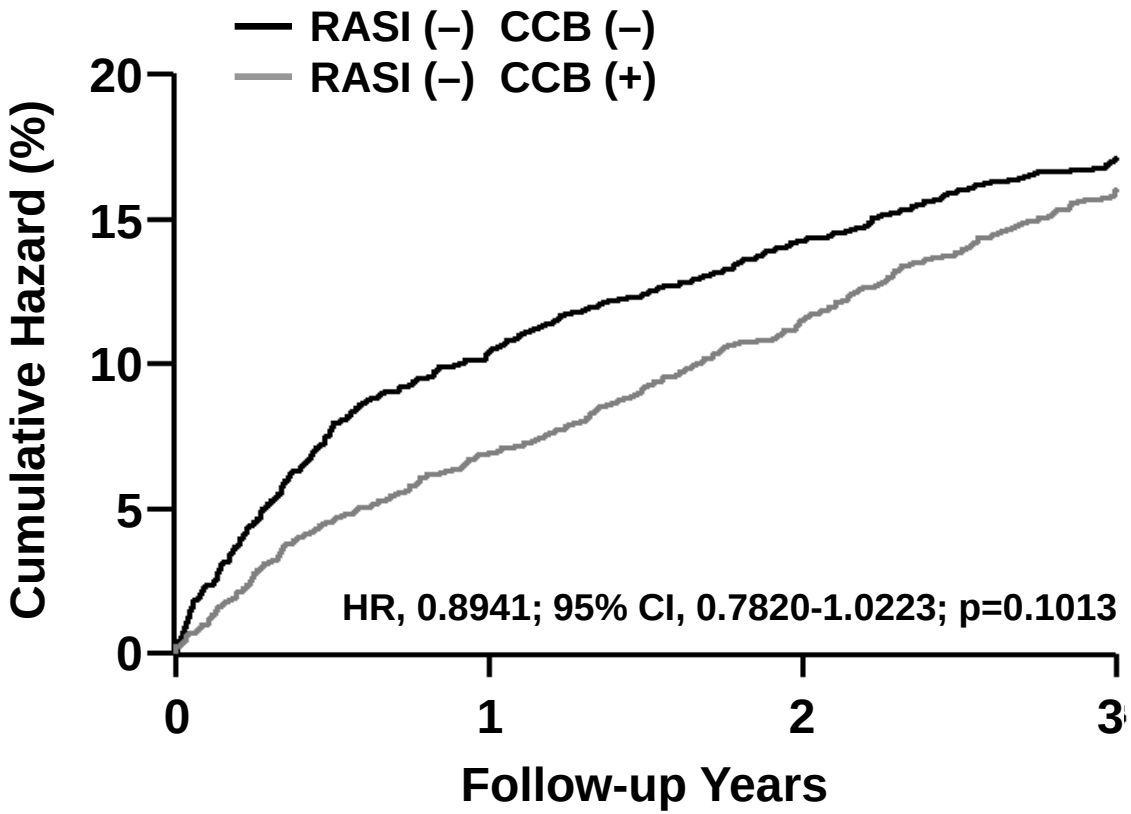
No. at Risk

RASI (–) CCB (–)	2,447	2,032	1,864	556
RASI (+) CCB (–)	2,447	2,113	1,915	757

No. of Events

RASI (–) CCB (–)	260	349	410
RASI (+) CCB (–)	171	268	325

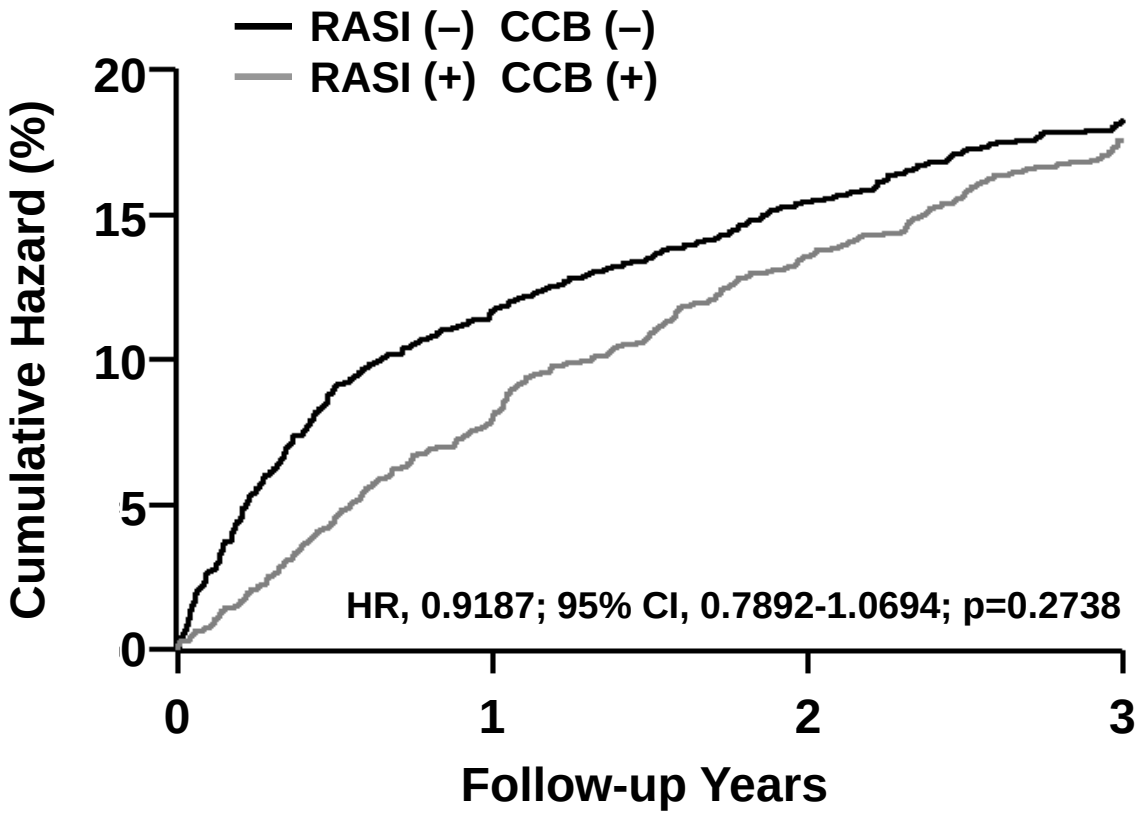
Figure 1-B



No. at Risk				
RASI (–) CCB (–)	2,659	2,230	2,043	609
RASI (–) CCB (+)	2,659	2,323	2,086	839

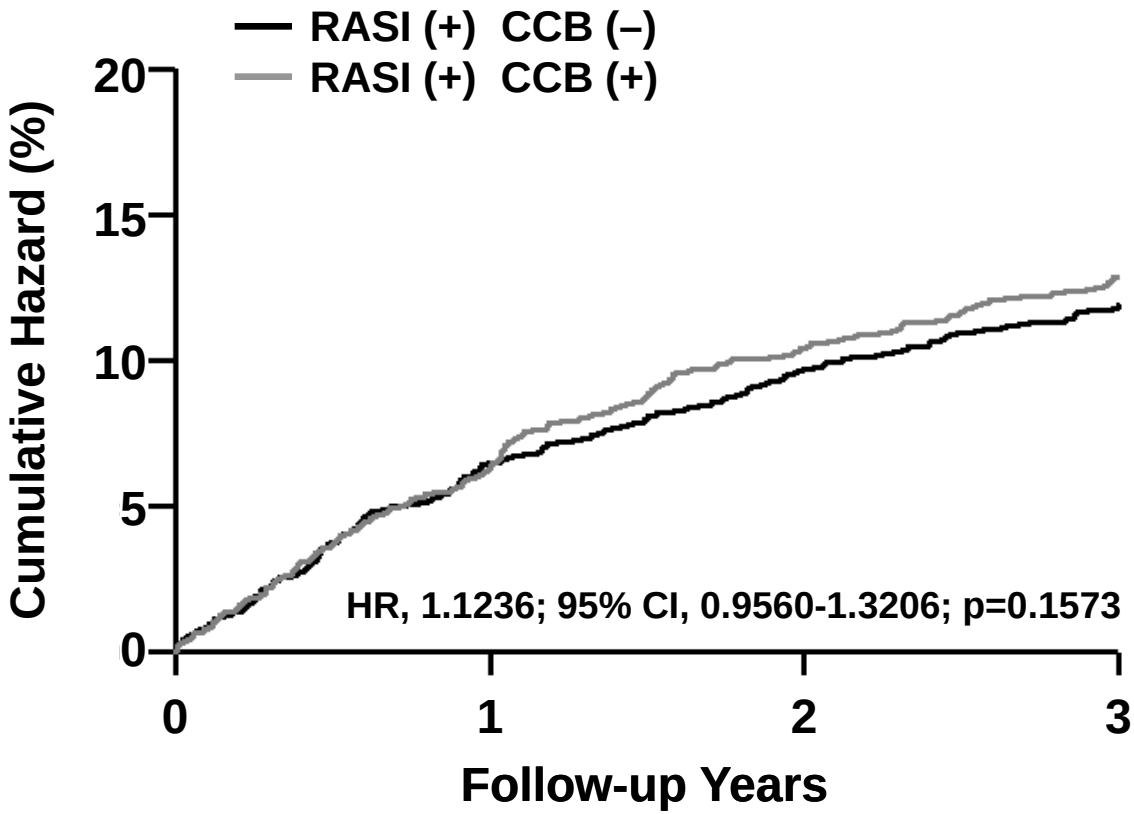
No. of Events			
RASI (–) CCB (–)	271	365	430
RASI (–) CCB (+)	181	292	394

Figure 1-C



No. at Risk				
RASI (–) CCB (–)	1,903	1,565	1,439	437
RASI (+) CCB (+)	1,903	1,629	1,459	574
No. of Events				
RASI (–) CCB (–)		218	283	329
RASI (+) CCB (+)		149	245	308

Figure 1-D



No. at Risk

RASI (+) CCB (–)	1,901	1,619	1,452	558
RASI (+) CCB (+)	1,901	1,642	1,467	587

No. of Events

RASI (+) CCB (–)	140	217	268
RASI (+) CCB (+)	142	238	299